OC-0451

Tumour volume, hypoxia and cancer stem cells as prognosticators for LRC after primary RCT in HNSCC

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Purpose or Objective: To investigate the impact of tumour volume, hypoxia and cancer stem cell (CSC) marker expression on outcome of patients with locally advanced head and neck squamous cell carcinoma (HNSCC) after primary radiochemotherapy.

Material and Methods: In this retrospective multicentre study, 160 patients with squamous cell carcinoma of the oral cavity, oropharynx and hypopharynx were included. All patients received primary cisplatin-based radiochemotherapy (RCT) between 2005 and 2011. Their median follow-up was about 26 months. Primary and nodal gross tumour volume (GTV) segmentations were performed centrally in the computer tomography-based radiation treatment plans. HPV status (p16 overexpression) and CD44 expression were analysed by immunohistochemistry. Gene expression analysis was performed for hypoxia-associated genes and the potential CSC marker SLC3A2. Results of the biomarker analyses, clinical parameters and tumour volume were correlated with the clinical outcome. Primary endpoint was loco-regional control (LRC). Secondary endpoints were distant metastases (DM) and overall survival (OS).

Results: In univariate analysis, tumour volume, HPV status and CSC marker expression were significantly associated with LRC (tumour volume: HR 1.51, p=0.02; HPV: HR 0.30, p=0.02; CD44: HR 2.30, p=0.04; SLC3A2: HR 2.08, p=0.01). Interestingly, hypoxia showed a significant association with LRC in small tumours only (HR 9.26, p=0.04). Multivariate Cox regression analysis including HPV status, tumour localisation, stage, smoking status, tumour volume and hypoxia or the respective CSC marker showed a significant effect of the tumour volume (HR: 1.6-1.8, p<0.01), SLC3A2 (HR 2.03, p=0.02) or CD44 (HR 2.52, p=0.04) on LRC. Tumour hypoxia also reached borderline significance in small tumours (HR 7.86, p=0.06). Interestingly, the tumour volume was an independent variable in all Cox models, a high tumour volume was significantly associated with poor LRC. Tumour volume and CSC marker expression also showed a negative prognostic impact on the secondary endpoints DM and OS.

Conclusion: We have shown that large tumour volume and high CSC marker expression correlate with poor LRC in patients with locally advanced HNSCC who received primary RCT. In small tumours, hypoxia also had a negative impact. After validation of these promising results in the ongoing prospective study of our study group, these biomarkers may help to further stratify patients for individualised treatment escalation or de-escalation strategies.

OC-0452

Prospective randomized adaptive dose-de-escalation in the elective neck: late toxicity and control

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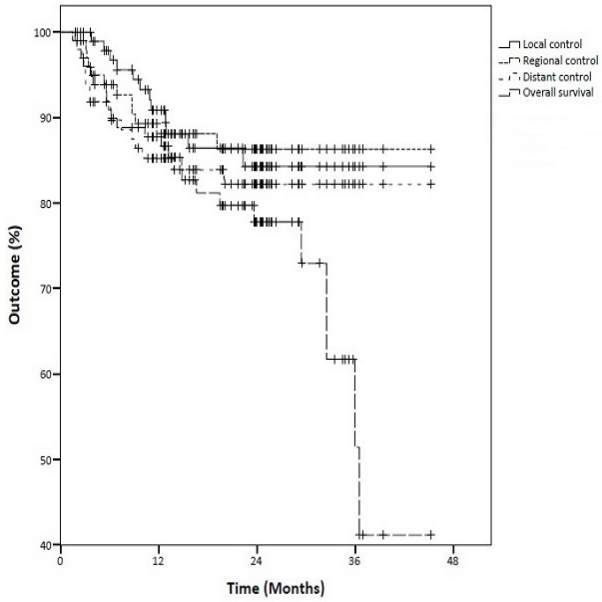
Purpose or Objective: A multicentre prospective randomized phase II trial investigated whether a 3-phase adaptive IMRT-scheme using reduced volumes of elective neck could reduce toxicity without compromising disease control compared to standard non-adaptive IMRT. We report on disease control and toxicity at 6 and 12 months of follow-up.

Material and Methods: All patients were primarily treated with IMRT ± chemotherapy for head and neck squamous cell carcinoma with a 2 Gy-equivalent dose of 40 Gy to the elective neck. The dose to the high-risk volume was not reduced. In the adaptive de-escalation (AD) arm, elective neck volumes were reduced based on a lower theoretical risk of subclinical disease and replanning was done after 2 and 4 weeks. In the control (C) arm, IMRT without adaptations and with standard volumes of elective neck was performed.
All statistics were performed using Fisher's exact test and Kaplan-Meier analysis (SPSS v. 23).

Results: Patiënts, tumor and treatment characteristics can be found in Table 1.
Before 1 year of follow-up, 12 patients deceased due to aspiration (n=1), tumor progression (n=8) or intercurrent disease (n=3).
At 6 months, we observed grade (G) ≥2 dysphagia in 3% and 6% (p = 1.0), G≥2 xerostomia in 40% and 34% (p = 0.81) and G≥2 fibrosis in 6% and 6% (p = 1.0) in the AD- and C-arm, respectively. At 12 months, we observed grade G ≥2 dysphagia in 17% and 3% (p = 0.09), G≥2 xerostomia in 43% and 28% (p = 0.28) and G≥2 fibrosis in 10% and 9% (p = 1.0) in the AD- and C-arm, respectively.
Local (LC), regional (RC) and distant control (DC) and overall survival (OS) for the whole group are given in Fig. 1. LC, RC, DC and OS were 86%, 84%, 82% and 74% in the AD-arm and 90%, 92%, 86% and 78% in the C-arm, respectively. All p-values were > 0.05. Regional relapse was observed in 8 (AD) and 4 (C) patients: 5/12 were isolated regional relapses (3 in the AD- and 2 in the C-arm) of which 3/5 isolated relapses were seen in the initial GTV of a pathological lymph node, 1/5 in the irradiated elective neck in the C-arm and 1/5 in the AD-arm in a region of the neck that would have been irradiated in the C-arm; salvage neck dissection was successfully performed. Seven regional relapses were combined with local recurrence (n=3) or metastases (n=4).

	AD-arm (n=50)	C-arm (n=50)	p-value
Age (range; in years)	63,0 (38-84)	62,4 (38-83)	
Male/female	39/11	42/8	0.61
Site: - Oropharynx - Hypopharynx - Larynx - Oral cavity	 24 13 10 3	 25 10 14 1	0.56
HPV-status oropharynx - Negative - Positive - Unknown	 5 4 15	 8 5 12	0.76
T-staging - T1 - T2 - T3 - T4a - T4b	 1 16 15 16 2	 3 12 20 12 3	0.55
N-staging - N0 - N1 - N2a - N2b - N2c - N3	 11 2 0 16 19 2	 11 6 1 16 15 1	0.58
Pre-IMRT neck dissection	5	5	1.00
Concomitant systemic therapy - Cisplatin-based - Cetuximab	30 29 1	29 27 2	1.00



Conclusion: With a minimal follow-up of 1 year, no significant differences in RC, LC or DC or OS were observed between adaptive IMRT with reduced volumes of elective neck versus standard IMRT with non-reduced volumes, although 1 patient had an isolated regional recurrence in the non-treated elective neck. Unfortunately, the volume reduction and adaptive strategy did not result in a better late toxicity profile. We hypothesize that due to the large portion of patients with locoregionally advanced disease the treated neck volumes could not be sufficiently reduced in the whole group to achieve the desired gain in toxicity. Future analysis will now be started to elucidate this problem.

OC-0453

Phase II trial of de-intensified chemoradiotherapy for HPV-associated oropharyngeal cancer

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Purpose or Objective: We performed a prospective multi-institutional phase II study of a substantial decrease in concurrent chemoradiotherapy (CRT) intensity as primary treatment for favorable risk, HPV-associated oropharyngeal squamous cell carcinoma (OPSCC).

Material and Methods: The major inclusion criteria were: 1) T0-T3, N0-N2c, M0, 2) HPV or p16 positive, and 3) minimal/remote smoking history. Treatment was limited to 60 Gy intensity modulated radiotherapy with concurrent weekly intravenous cisplatinum (30 mg/m2). The primary study endpoint was pathologic complete response rate (pCR) based on required biopsy of the primary site and dissection of pretreatment positive lymph node regions, regardless of radiographic response. Power computations were performed for the null hypothesis that the pCR rate is 87% and N=40, resulting in a type I error of 14.2%. Secondary endpoint measures included physician reported toxicity (CTCAE), patient reported symptoms (PRO-CTCAE), quality of life